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RENAL CHANGES ASSOCIATED WITH LIVER DISEASE

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Rokitansky in 1842 was the first to draw attention to the renal lesions of patients who had died of liver disease. Since his fundamental studies, cholemic nephrosis, a renal injury accompanying severe jaundice, has become a generally accepted concept. Renal changes subsequent to hepatic diseases, had at first been ascribed to the increased bilirubin level in the blood; some authors explained the injury of the kidney with the toxic effect of proteins liberated from the damaged liver, while others ascribed it to the reflex-mechanism existing between the two organs, or to the reduced detoxicating capacity of the liver [8, 2, 6, 7, 12, 13, 21, 3, 18, 24].

Nonnenbruch classed the hepato-renal syndrome among the extrarenal azotaemias. He found that hyposthenuria and oliguria may develop and that urea is responsible for the eventual rise of the non protein nitrogen level in the blood. Recently a number of authors [11, 25, 26, 27, 1] have emphasized the decisive influence, the disturbed metabolism of extrarenal proteins exerts on the development of nephrosis considering that the liver plays the most important part in breaking down and synthetizing proteins. *Wuhrmann* regards the hepatic change leading to dysoria as a main problem of the hepatorenal syndrome, and even of the nephrosis syndrome.

While a severe degeneration of the tubular system accompanies the diseases of the liver, in recent years only a few authors [23, 4, 10] have mentioned coincident glomerular lesions. According to recent knowledge regarding nephroses, it appears to be necessary that renal changes, due to liver disease, i. e. the renal factor of the hepatorenal syndrome, should be investigated anew.

Examinations

Regarding above mentioned data, renal changes associating various kinds of liver disease have been examined in 50 cases. Organs of young subjects were selected for examination in the first line, care having been taken to exclude renal lesions arising from sources other than hepatic. The kidneys were examined in 17 cases of acute liver disease, such as hepatitis and yellow atrophy; in 20 cases of chronic liver disease, such as chronic hepatitis and cirrhosis of different origin; in 6 cases of central liver necrosis consequent upon congestion; finally in 7 cases of biliary duct or liver cancer in which clinical diagnosis had revealed grave obstructive jaundice and at autopsy focal necroses were found in the liver. Systematic

clinical examinations of renal function had not been made in all cases,so that the failure of renal function had usually been inferred only from albuminuria, the rise in the non protein nitrogen level, oedema, oliguria or anuria. On the basis of such symptoms, renal lesion had been suspected during life in 45 per cent of the cases and, in approximately 25 per cent of the cases, thorough examinations (estimations of clearance, glomerular filtrate) had confirmed the existence of a disturbance of renal function. As a rule, hepatorenal syndrome was clinically diagnosed in these instances. In the histological studies, staining was made with haematoxyline-eosin, van Gieson, Sudan, Heidenhain's azocarmine, Mallory's connective tissue dye, Unna-Pappenheim's methyl green-pyronin (to indicate albumin-like proteins), and finally, Weigert's fibrin stain.

Renal injury in cases of fulminant hepatitis

In 17 out of the 50 cases examined, death was caused by acute fulminant hepatitis. Hepatorenal syndrome had been clinically diagnosed in 5 instances, where renal symptoms had aggravated the liver disease. Autopsy and biopsy changes in cases without previous renal function tests were not different from those observed in cases, where clinical symptoms had pointed to a renal injury.

The capsule of the enlarged, swollen kidney strips easily ; the organ is of a flaccid, succulent, sometimes brittle consistence, its colour — dependent on the graveness of the jaundice— is characteristically brownish-yellow, bordering on green. The cortical substance is somewhat broader than usual. Biopsy revealed the picture usual in cholaemic nephrosis, i. e. severe tubular changes in every one of the 17 cases. The lumen of the collective tubules were found to be filled with granular clots and bile pigment casts. Granules of this greenish brown pigment are present also in the epithelial cells of the proximal convoluted tubules and Henle's loop. Most conspicuous is the lipoid, or eventually parenchymatous degeneration of the tubules, sometimes manifesting itself in the form of necrotising nephrosis. In addition to the present cases, we observed in one instance vacuolar (Fig. 1), in another instance hydropic degeneration of the tubules ; in several cases droplets staining red or, exceptionally, blue with Mallory's dye, had been demonstrated in the epithelial cells of the convoluted tubules (hyaline droplet degeneration). In the kidney of a 6 weeks old infant with grave liver necrosis there had been occlusion bodies in the nucleus of the epithelial cells of the proximal convoluted tubules. This change is characteristic of inclusion disease of infants, cytomegalia infantum.

In view of the findings pointing to an extreme importance of the glomeruli in the genesis of nephrosis, we have subjected to examination the capillary system of the kidney, the glomeruli, arterioles and the interstitial tissues. It was found that in 16 out of 17 cases of fulminant hepatitis examined, acute glomerular changes, and in 5 cases acute arteriolar lesions were present. The glomeruli were enlarged, swollen beyond their usual size. Within Bowman's capsule around the glomerular tuft protein precipitated in clots or formed a homogeneous mass (Fig. 2). The wall of the glomerular capillaries were thickened ; they stained a homogeneously bright red with Mallory's dye, while, in

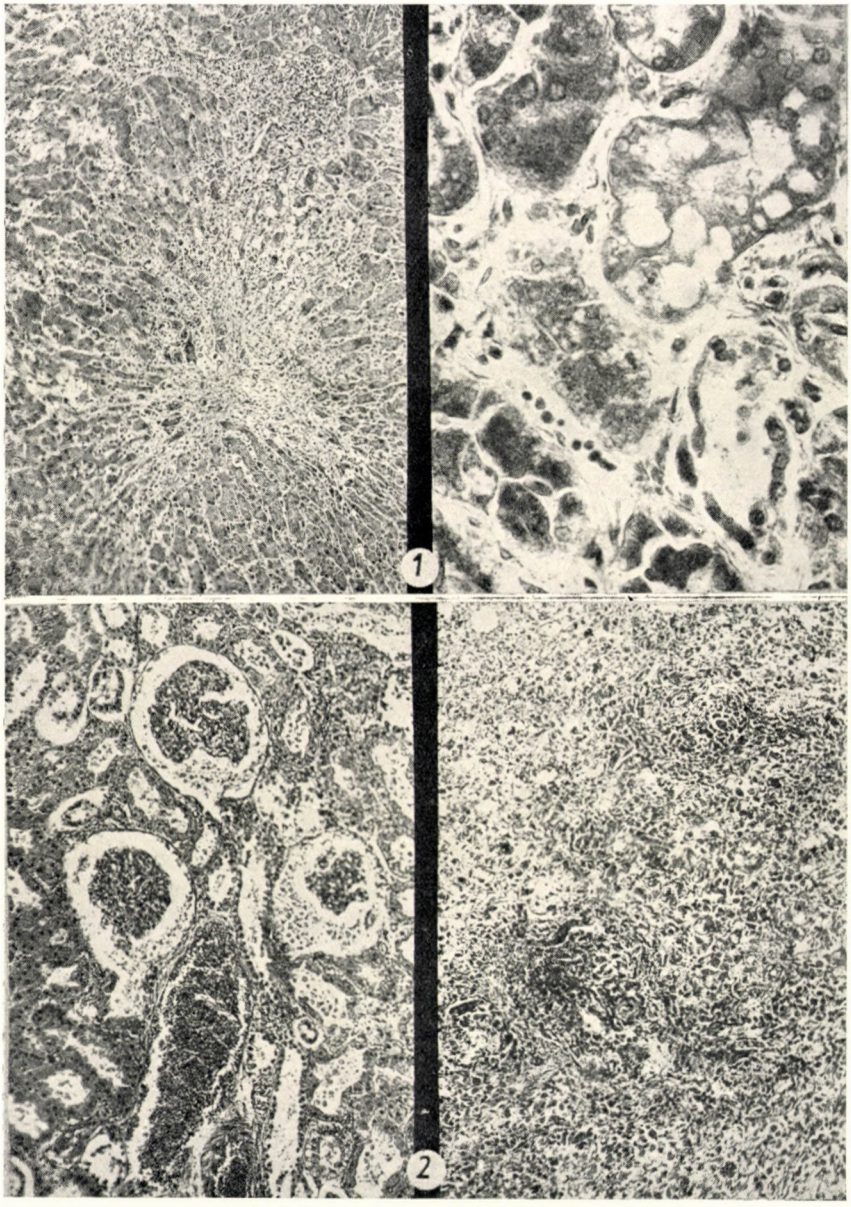

Fig. 1. Left, focal hepatic necrosis and round cell infiltration; right, vacuolar degeneration of the renal tubular epithelium of the same case. (Female, 37 years. Clinical diagnosis: hepatorenal syndrome. Autopsy protocol No. 1516/952)

Fig. 2. Right, picture of totally destroyed liver; left, flake-like extracapillary precipitate in the cavity of Bowman's capsule. (Female, 25 years. Clinical diagnosis: acute hepatitis. Autopsy prot. No. 185/951)

other cases, Weigert's fibrin stain revealed fibrinous imbibition (fibrinoid necrosis) of the basement membrane of the glomerulus of the glomerular capsule and of the tubules (Fig. 3). In cases with a slower course the mesoangium is broadened and imbibed with albumin, the basement membrane is thickened. Methyl green pyronin stain reveals the presence of protein casts in the tubules, and protein is found also in the interstitial tissue, especially around the glomeruli. In 5 cases, the small arterioles of the kidney stained uniformly red with eosin, and fiery red with Mallory's dye, exhibiting arteriolar necrosis (Fig. 4).

Changes of the kidney in cirrhosis

In cases of chronic hepatitis and cirrhoses of various origin, the morphology of the kidney may be similar to the picture seen in acute cholaemic nephrosis. This was found in 11 of the 20 chronic cases examined, whereas in 9 instances gross examination revealed a fine granulation on the surface. Microscopically swollen glomeruli are found side by side with shrunken hyaline ones (Fig. 5). A proliferation of the capsular epithelium can frequently be observed, and thickening of the glomerular basement membrane is also common. In addition to the chronic changes described, acute processes such as fibrinoid necrosis of the glomerular tufts or albuminous imbibition of the basement membrane of the capsule and the tubules, were observed in numerous cases ; in other instances protein and bile pigment casts, as also storage of bile pigment, were encountered. Grave degeneration of the proximal convoluted tubules and Henle's loops was present in all cases, while hydropic degeneration was met with in one, and interstitial round cell inflammation in two of our 20 cases examined. Proliferation of connective tissue between the collecting tubules (intertubular fibrosis) is often encountered in cases associated with chronic hepatitis. In the 5 cases of hepatic cirrhosis the renal arterioles were thickened and their walls stained a homogeneous violet-blue with Mallory's dye, undoubtedly due to the presence of accumulated hyaline substance.

According to the above, in cases of hepatic cirrhosis acute renal changes are also present beside chronic ones.

Renal lesions in jaundice of subjects with heart disease

The kidneys of 6 subjects were examined who died of heart failure and in whom enlargement of the liver and positive liver function tests had been demonstrable during life. In 2 out of the 6 cases hepatitis had been the clinical diagnosis. Grossly, extensive central necroses and haemorrhage characterized every one of the cases. Apart from the usual changes due to congestion, the

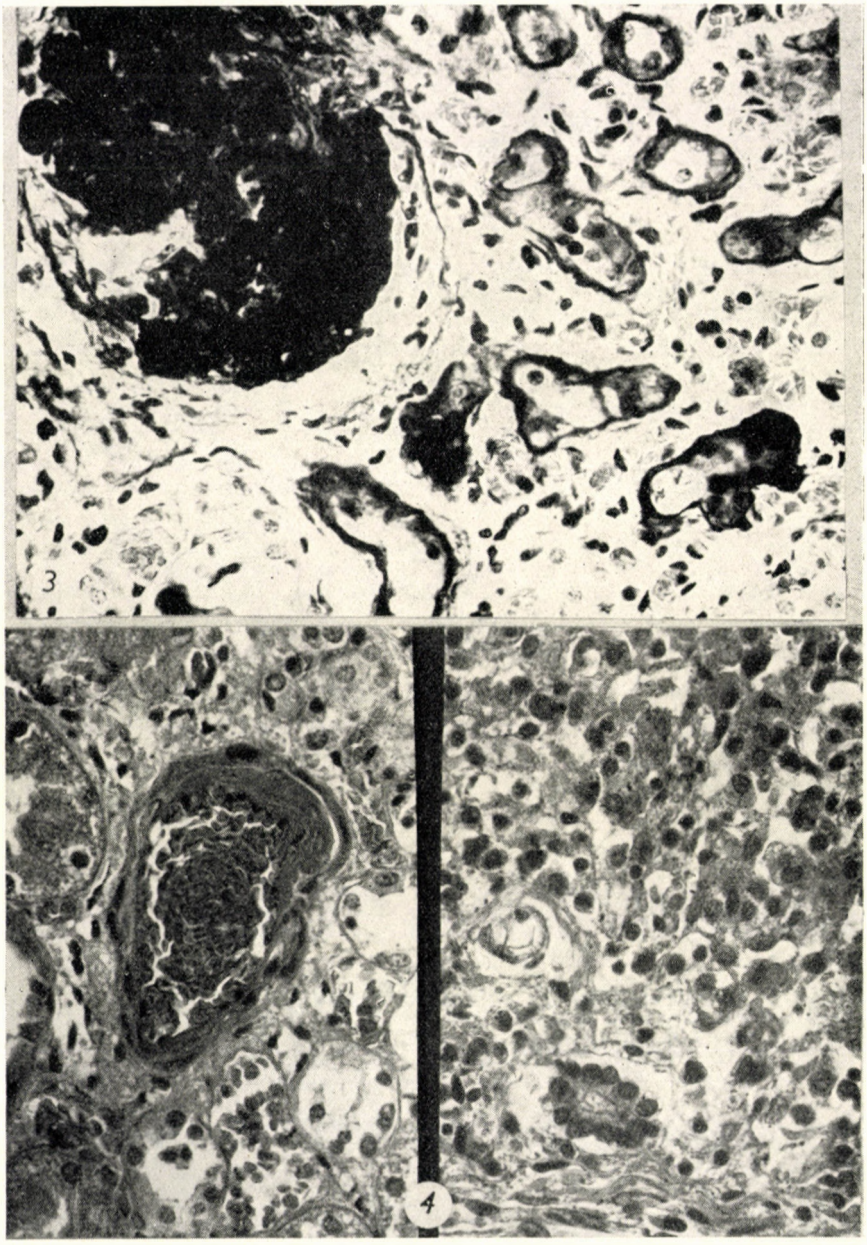

Fig. 3. Fibrinous imbibition of the basement membrane of the glomerular tufts and the proximal convoluted tubules. (Male, 43 years. Clinical diagnosis : acute yellow atrophy of the liver. Autopsy prot. No. 172/951. Weigert's fibrin stain)

Fig. 4. Right, liver of a 24 years old man, died with fulminant hepatitis ; left, arteriolar necrosis in the kidney. (Autopsy prot. No. 118/951)

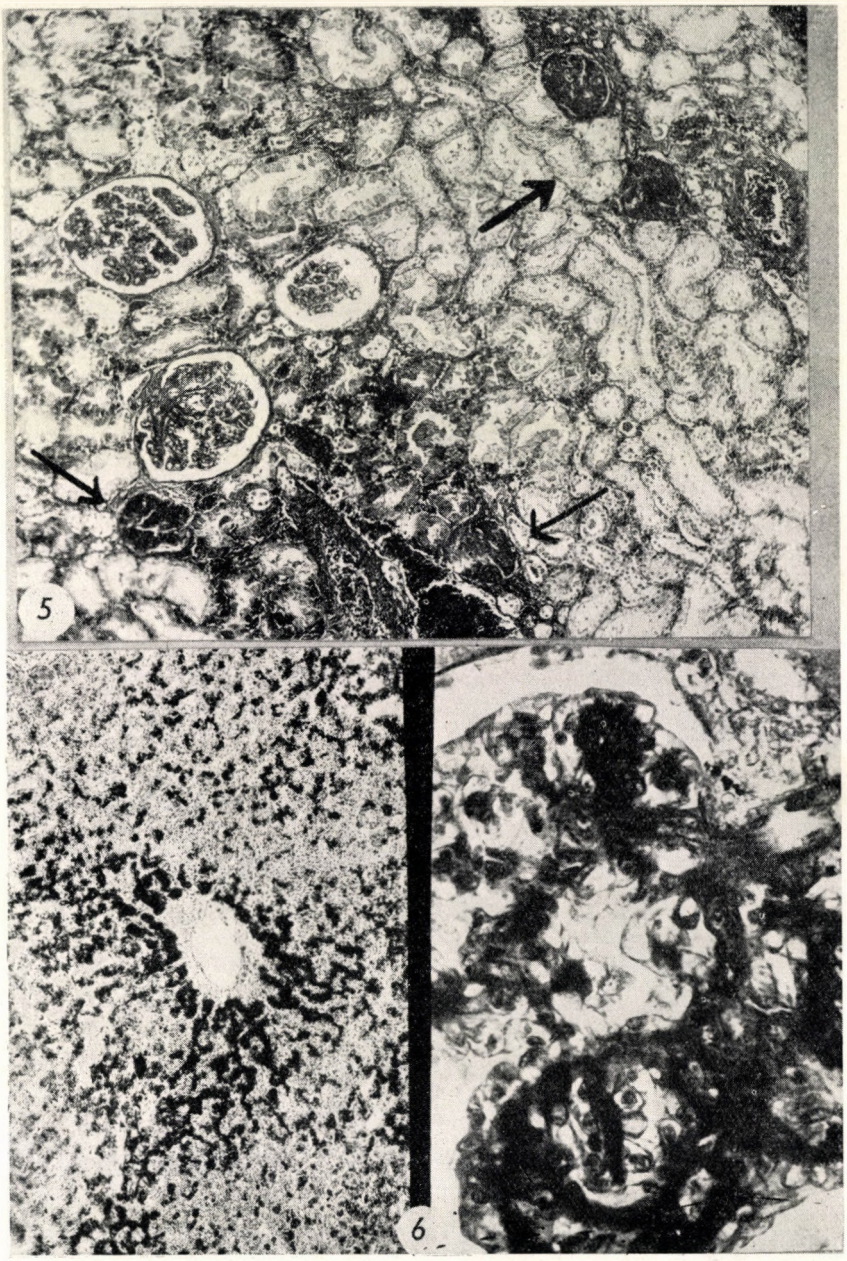

Fig. 5. Man, 39 years old, died with liver cirrhosis (Autopsy Prot. No. 1/952). Next to glomeruli showing hyaline degeneration, glomeruli indicating compensatory hypertrophy can be seen. *Fig. 6.* Left, a case of central hepat c necrosis, where degenerated liver cells contain lipoid droplets. (Sudan III. stain). Right, glomerulus with marked thickening of basement membrane. (Male, 38 years. Clinical diagnosis: Vitium cordis. Hepatitis? Autopsy prot. No. 267/951)

kidneys revealed the same changes as in acute and chronic hepatic disease. Especially characteristic of this type of renal lesion was, however, the thickened glomerular basement membrane, a phenomenon encountered in every case (Fig. 6). Sometimes fibrinoid necrosis of the glomerular tufts was also present. The tubules presented parenchymal, fatty, and, in one instance, vacuolar degeneration. In no case was a lesion of the renal arterioles observed.

Renal lesion in jaundice due to diseases or carcinoma of the biliary ducts

The discussion of renal lesions would remain incomplete if it did not treat of the deleterious effect exerted on the kidney by diseases of the biliary duct and cancer of the liver. Severe jaundice was present in every one of the 7 cases examined. Microscopically we found extensive zonal necroses. Notwithstanding the fact that there was but one single case in which during life symptoms had pointed to renal disease, the morphological picture in every one of the 7 cases displayed features resembling in every point those discussed in the foregoing paragraphs. Renal injuries were found to be independent of the degree of jaundice. Acute arteriolar necrosis occurred in 4 instances out of the 7 (57%).

TABLE I

Type of hepatic lesion	Number of cases examined	Age	Clinical renal symptoms						Morphologically demonstrated change of			
			Oedema oliguria anuria	Albuminuria	Dilut. Concentr.		RN.		glomeruli		tubules	arterioles
					number of cases examined	disturbance	number of cases examined	increased	acute	chronic		
Acute fulminant hepatitis	17	From 9 months to 47 years	5	10	4	4	8	5	16	—	17	5
Cirrhosis	20	From 7 to 60 years	11	7	7	6	7	6	11	9	20	5
Cardiac failure with jaundice	6	From 12 to to 55 years	4	3	—	—	2	2	—	6	6	—
Carcinoma of biliary duct or liver with jaundice	7	From 42 to 64 years	1	1	—	—	1	—	4	3	7	4

Discussion

From the findings in 50 cases, the conclusion may be drawn, that both acute and chronic hepatic disease, including central necrosis of cardiac origin,

as well as liver necrosis, due to carcinoma of the biliary ducts, may give rise to severe renal changes. Microscopical examination confirmed the existence of a renal lesion in cases, where grave renal disturbances had been observed during life and also in cases, where clinical manifestations had been limited to a mild form of albuminuria. This type of renal lesion differs from the well-known morphological picture associated with cholaemic nephrosis; beside grave changes of the tubular system (parenchymal, lipoid, vacuolar, hydropic, hyaline droplet degeneration) and interstitial inflammation, severe injury could be demonstrated also on the glomeruli, renal arterioles and on the tubular basement membrane. It was found that whereas acute hepatic disease is associated not only with tubular degeneration but, in 94 per cent of the cases, also with acute glomerular and arteriolar changes (necrosis of the glomerular capillaries, necrosis of the arterioles, albuminous imbibition of the basement membrane of the glomeruli, etc.), chronic hepatic disease is not necessarily followed by such renal lesions. Cirrhosis and chronic renal changes (hyalinisation of glomeruli and arterioles, interstitial fibrosis, casts, etc.) concur in 45 per cent of the cases, but acute lesions of the glomerular tufts, arterioles and the tubular epithelium may also occur. It was revealed in the course of this study, that acute exacerbations during chronic liver disease may produce repeated acute renal damage; and also that while epidemic hepatitis or homologous serum jaundice is followed by acute renal lesions only, a chronic renal lesion may ensue once the liver damage has become chronic.

Changes occurring in the kidney in case of central liver necrosis or of hepatic lesion due to biliary duct cancer combined with jaundice, were found to be similar in every respect to the renal changes associated with acute and chronic hepatitis. While a thickening of the glomerular basement membrane seems to occur most frequently in acute and chronic hepatitis, acute arteriolar necrosis is observed comparatively often in the former group.

The results described are in accordance with the recent theories of nephrosis. *Fahr* in 1925 studied the damage of glomerular capillaries in nephrosis. His findings have been confirmed by *Randerath* who, proving that in nephrosis the permeability of glomerular capillaries is increased, has regarded nephrosis as a primary affection of the glomeruli. *Rusznyák* and *Németh*'s opinion is, that albuminuria is due to increased permeability of the glomerular tufts. According to the investigations of *Zollinger*, every kind of nephrosis may be regarded as a glomerulo-tubulo-nephrosis.

The most frequent changes encountered in the kidney in connection with acute and chronic liver disease were coagulated protein in Bowman's capsule and albuminous imbibition of the glomerular, capsular and tubular basement membrane and that of the renal arterioles. There were protein casts in the tubules and often a hyaline droplet degeneration of the tubular system as a consequence of the disturbed balance of the secretory-resorptive system

[14]. Staining with methyl green pyronin revealed the presence of protein also in the interstitial tissue. Phenomena of this kind are indicative of a disturbance in both, the protein metabolism of the organism and in capillary permeability. The correctness of this concept is confirmed by the findings of *Wuhrmann* and *Oettel* who have found a change in the correlation of plasma proteins in hepatic lesions (para- or dysproteinaemia). They ascribe the renal lesions to the disturbance of protein metabolism arising in consequence of hepatic disease.

The problem, whether the altered permeability of capillaries is a consequence of a toxic degeneration, or of vasoconstrictive ischaemia due to a disturbance of the nervous system, could not be settled. It may, however, be established in agreement with a few other data [4, 10, 5] that renal changes, associated with acute or chronic liver disease, cholaemic nephrosis, cannot be regarded as isolated tubular nephrosis but belongs to the group of glomerulonephrosis [16].

The finding that a more or less grave renal lesion, glomerulonephrosis, accompanies every kind of liver disease, throws new light on the problem of the hepatorenal syndrome. Following *Nonnenbruch*, the term hepatorenal syndrome is applied whenever the course of an inflammatory, traumatic, or toxic liver disease is aggravated by concomitant renal lesions. Our own investigations indicate that a careful clinical study will reveal renal lesions in most cases of hepatic disease. The same conclusion was drawn from clinical observations by *Szabó*, *Zsoldos* and *Rév* as well as by *Siegler* and *Faludi*. The two teams, independently of one another, made a study of renal function in patients with hepatitis and found failure in both the clearance and the glomerular filtration rate. Similar statements have been made also by *Siede*.

Hepatorenal insufficiency following abdominal operations, form another large group of simultaneous hepatic and renal disease. We could observe mild liver injury with acute renal changes in cases of this kind. Considering the slightness of the hepatic lesion in these cases, they cannot be classified among other liver diseases associated with renal lesion.

It may be concluded from the above that the term hepatorenal syndrome is a clinical concept. The pathohystological renal lesions observed in cases of clinically diagnosed hepatorenal syndrome do not differ from renal changes associated with other types of liver disease except with its increased gravity. Independently of clinical manifestations, every kind of liver injury results in the same characteristic morphological pattern in the kidney, that of glomerulo-tubulo-nephrosis.

Summary

Renal lesions associated with liver disease have been subjected to autopsy and biopsy examination in 50 cases. Whether or not there had been clinical symptoms of renal damage during life, in cases of acute or chronic hepatitis, central necrosis due to congestion, further in diseases of the biliary system and carcinoma of the liver we could find in the kidney glomerulo-tubulo-nephrosis. Acute hepatic damage is associated with acute renal lesions, while chronic hepatic diseases may be the cause of chronic renal changes. Apart from tubular injuries, acute and chronic lesions of the glomerular tufts and arterioles were observed in such cases. These findings justify the classification of cholaemic nephrosis among the group of glomerulonephrosis. In view of the fact that every important disease of the liver is associated with more or less morphologically demonstrable renal damage, the hepato-renal syndrome may be considered as exclusively clinical concept.

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ДАННЫЕ К ВОПРОСУ ГЕПАТО-РЕНАЛЬНОЙ СИНДРОМЫ

Я. Ласло и М. Гаал

Резюме

Тяжелое, сопровождающее печеночные заболевания и поражающее исключительно почечные канальцы изменение стало известно под названием »холемического нефроза«. В свете современных взглядов на существо нефроза мы считали нужным пересмотреть вопрос о поражении почек, сопровождающем желтуху, т. е. вопрос о почечном факторе гепато-ренальной синдромы.

Мы исследовали в 50-и случаях изменения почек, сопровождающие заболевания печени. Среди наших случаев имелись острый и подострый, далее хронический гепатит,

и кроме того некроз центральной части печеночной дольки вследствии застоя сопровождающиеся изменениями почек. Нам удалось установить, что кроме тяжелых изменений системы канальцев (жировое, вакуольное паренхиматозное перерождение) значительные изменения наблюдаются и в почечных клубочках.

Внутри капсулы Боумена мы нашли внекапиллярный белковый сверток, — наблюдалось бельковое пропитывание клубочков, капсулы Боумена, и основной оболочки канальцев.

Установлено бельковое пропопитывание мельких почечных артерий и наличие белкового осадка в просвете более крупных почечных сосудов. Белок, находящийся внутри просвета сосудов проявлялся в капиллярах клубочек в виде эмболов. Канальцы часто оказались наполненными многоцветными цилиндрами белковой природы. При хронических заболеваниях, печени и изменения почек носили хронический характер : наблюдалось расширение мезангия клубочек, гиалинизированные клубочки, и фиброз промежуточной соединительной ткани. В некоторых случаях мы нашли промежуточное гигантоклеточное воспаление почек.

Описанные явления указывают на нарушение обмена белковых веществ организма и изменения проходимости. Мы разделяем взгляды авторов, считающих что решающим фактором в этиологии нефроза является внепочечное нарушение белкового обмена веществ. По нашему мнению вследствие заболевания печени, нарушается белковый обмен веществ, стоящии бессомненно под направляющим действием центральной нервной системы, и это нарушение ведет к возникновению и почечных изменений.